(d) reacting the deprotected 5'-hydroxyl with an 5'-protected activated phosphorus compound to produce a covalent linkage therebetween;

(e) oxidizing or sulfurizing the covalent linkage to form a phosphodiester, phosphorothioate, phosphorodithioate or H-phosphonate linkage;

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(f) repeating steps c through e at least once for subsequent couplings of additional activated phosphorus compounds, to produce the completed phosphorus-linked oligomer; and

(g) cleaving the oligomer from the solid support;

wherein steps (b) through (f) are performed with an automated device;

wherein said oligomer is a linear oligomer.

REMARKS

Claims 1-42 are pending in the present application.

Claims 1-42 are rejected under 35 U.S.C. §101 as allegedly containing an improper definition of the process. While "performed using an automated device" and "performed with an automated device" connote the same meaning, Applicants have adopted the latter language suggested in the Office Action to further prosecution.

Claims 1-41 are rejected as allegedly being indefinite under 35 U.S.C.§112, second paragraph. The Office Action alleges that claims 1 and 21 recite a broad definition "comprising a protic acid in a solvent" with a narrow definition "the solvent being an aromatic solvent,...." Applicants have amended claims 1 and 21 to further clarify that the solvent "consists essentially of an aromatic solvent, an alkyl aromatic solvent, a halogenated aromatic solvent, a halogenated alkyl aromatic solvent, or an aromatic ether solvent." Applicants believe that this removes any ambiguity.

Claims 1-42 are rejected as allegedly anticipated under 35 U.S.C.§102 by Horn, et al., Nucleic Acids Research 1997, 25, 4842-4849 (PTO-892 ref. UA). Applicants traverse this rejection. A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently, in a single prior art reference. Verdegaal Bros. v. Union Oil Co. of Calif., 814 F.2d 628, 631 (Fed. Cir. 1987); MPEP § 2131. The identical invention must be shown in as complete detail as is contained in the claim. Richardson v. Suzuki Motor Co., 868 F.2d 1226, 1236 (Fed. Cir. 1989); MPEP § 2131. The UA reference, however, does not disclose each step of the instant claims. For example, the UA reference does not disclose the "cleaving the oligomer from the solid support" element of claims 1, 21, and 42. Further, applicants note that the Office Action (page 4 of the July 30, 2002 Office Action) refers to "the generic character of the remainder of claims 1, 21, and 42" without making a specific showing of inherency. For at least these reasons, applicants request that the rejection be withdrawn.

Claims 1-42 are rejected under 35 U.S.C.§103(a) for alleged obviousness over U.S. Patent No. 5,705,621 to Ravikumar ("Ravikumar", PTO-892 ref. A) in view of U.S. Patent No. 4,973,679 to Caruthers et al. ("Caruthers", PTO-892 ref. G) and further in view of U.S. Patent No. 5,548,076 to Froehler et al. ("Froehler", PTO ref. H) and further in view of Sproat et al. (PTO-892 Ref. W), Conway, et al. (PTO-892 Ref. Y), Atkinson et al. (PTO-892 Ref. Z), and Sproat et al. (PTO-892 Ref. RA). Applicants respectfully request reconsideration and withdrawal of the rejection.

As best understood by Applicants, the Office Action asserts that the primary references (Ravikumar, Caruthers and Froehler) show a variety of solvent systems for 5'-deprotection, and do not indicate that the selection of any particular solvent system is critical. Thus, according to the Office Action, the references "motivate the selection of practically any solvent mixtures which will dissolve the reactants and not

otherwise interfere with the intended synthetic transformation." Page 9 of the July 30, 2002 Office Action. Applicants respectfully disagree, and discuss each of the primary references in turn.

1. The Ravikumar Reference

The Office Action asserts that this reference (and three additional Caruthers patents therein, listed on the form PTO-892 as references I, J and K), disclose conventional oligonucleotide synthesis. The Office Action states that the Ravikumar reference describes acid-mediated 5'-hydroxyl deprotection at col. 10, lines 10-16 and col. 14, lines 5-28, but fails to provide a preferred solvent for the deprotection, and concludes from this that the reference teaches that "[t]he choice of any particular deprotection solvent is a choice within the purview of the ordinary practitioner." Page 6 of the July 30, 2002 Office Action. However, Applicants respectfully assert that the Office Action reads into the Ravikumar reference a teaching that does not exist. As the Office Action points out, the Ravikumar reference is a patent document which discloses the use of a novel phosphorus protecting group for oligonucleotide synthesis. As such, the Ravikumar reference is not directed to any particular 5'-hydroxyl deprotection regime. It does not specify any particular 5'-deprotection solvent for use in its methods. The Ravikumar reference's silence in this regard is intended to convey only that the Ravikumar invention will work with any solvent *that is suitable*, but does not say anything about the *scope* of solvents that *are* suitable.[1] Thus, the Ravikumar reference does not support the contention of the Office Action.

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[1] As the Office Action points out, the Examples of the Ravikumar reference describe deprotection with dichloroacetic acid in dichloromethane. Page 6 of the July 30, 2002 Office Action. However, this fact also says nothing about the scope of deprotection solvents that are generally suitable for oligonucleotide synthesis.

2. The Caruthers Reference

The Office Action asserts that this reference teaches at col. 5, lines 10-14 the use of "... any solvent which will dissolve the reactants ...". Page 6 of the July 30, 2002 Office Action. While the Office Action admits that "[t]he context of this statement suggests that Caruthers was making reference to the coupling step", the Office Action nevertheless asserts that "the same generic teaching appears to also apply to the deprotection step". *Id.* The Office Action bases this assertion on the further assertion that the Caruthers reference discloses four deprotection reagents ($ZnBr_2$ in nitromethane; toluenesulfonic acid in chloroform:methanol; ZnBr2 in nitromethane:methanol; and 80% acetic acid), allegedly not considering any particular deprotection regime to be critical. However, Applicants respectfully assert that the Caruthers reference, read in its entirety, does not provide the broad teaching asserted by the Office Action, and in fact only teaches a narrow deprotection regime.

Applicants first note that the portion of the Caruthers reference at col. 5, lines 10-14, and cited by the Office Action, does not merely suggest, but rather explicitly refers to the coupling reaction. Contrary to the assertion of the Office Action, there is nothing in the reference that suggests the use of "any solvent" for the deprotection reaction.

Further, the Caruthers reference cannot be fairly be said to teach to the skilled artisan any deprotection regime other than a Lewis acid, preferably $ZnBr_2$, in a nitromethane or nitromethane:methanol solvent. The Caruthers reference explicitly states that it's method "is predicated on color formation by triarylmethyl cation in the present of an acid, whether a Lewis acid or a protic acid." Caruthers at col. 6, lines 26-28. The Caruthers reference further states in Example 4, col. 14, lines 4-11, that when protic acids are used "3-5% depurination of each purine by protic acids is observed even when the amount of acid is reduced to the minimum amount needed to remove the dimethoxytrityl

group." Indeed, the use of toluenesulfonic acid in chloroform:methanol for deprotection shown in Caruthers Table V, cited by the Office Action, is only intended to show protic acid hydrolysis rates for various trityl groups. In this regard, the Caruthers reference states at col. 15, lines 51-61:

> Several of the triarylmethylchlorides were condensed with the 5' hydroxyl of appropriately protected deoxynucleosides. These compounds are listed in Tables IV and V. The 5'-triarylmethyldeoxynucleosides were treated with protic and Lewis acids using carefully controlled conditions. The results of these studies are also recorded in Tables IV and V. These results show that several triarylmethyl groups forming different colors in acid solutions are hydrolyzed at approximately the same rapid rate in the presence of ZnBr2. **The rates are more variable -with [sic] protic acids.** (emphasis added)

The Caruthers reference teaches away from such variability in deprotection rate (and therefore the toluenesulfonic acid in chloroform:methanol cited by the action) at col. 16, lines 22-28, stating:

> [t]he various color coded triarylmethyl groups should preferably by hydrolyzed at approximately the same rate. Otherwise, each addition cycle must be individually monitored ..."

Thus, the art skilled, reading the Caruthers reference, would not understand the Caruthers reference to teach toluenesulfonic acid in chloroform:methanol, or any other protic solvent or solvent system therefor, such as is recited in the present claims.[2]

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[2] Applicants assert that for this reason alone, the present claims cannot be obvious in view of the Caruthers reference.

The Office Action further cites the Caruthers at col. 19, lines 47-50 as teaching deprotection with 80% acetic acid. However, that passage does not refer to the deprotection of a support-bound species having its appended protecting groups, but rather describes the 5'-terminal deprotection of a completed deoxyoligonucleotide that had already been removed from the solid support, and which also had been subject to additional deprotection to remove amino protecting groups. Further, as stated above, the Caruthers reference teaches away from the use of such protic acids. Thus, the skilled artisan would not understand the Caruthers reference to teach deprotection of a support bound oligonucleotide with 80% acetic acid.

In view of the discussion above, it can be seen that the only teaching of 5'-triarylmethyl deprotection in the Caruthers reference is the use of a Lewis acid, preferably $ZnBr_2$, in nitromethane or nitromethane:methanol solvent. There is therefore no basis for the assertion that the Caruthers reference motivates "any solvent" for deprotection.

3. The Froehler Reference

The Office Action asserts that this reference teaches a "whatever works best" philosophy, citing the Froehler reference at col. 5, lines 26-28 and lines 38-47. Page 7 of the July 30, 2002 Office Action. However, the passage at col. 5, lines 26-28 reads in full:

> The solvent **for the condensation reaction** is an anhydrous organic solvent, preferably anhydrous pyridine/acetonitrile in volume proportions of 1:1. (emphasis added)

Thus, this passage explicitly refers to the condensation reaction. The Office Action further states:

> This "whatever works best" philosophy apparently also applies to the deprotection step; see column 5, lines 38-47. The last line of this portion of column 5 is particularly instructive. After listing 3 (three) different deprotection reagent/solvent mixtures, Froehler suggests a very flexible

> "whatever works" approach by further stating that "[o]ther deprotection procedures suitable for other known protecting groups will be apparent to the ordinary practitioner."

The July 30, 2002 Office Action at page 7. However, the cited passage of Froehler recites:

> The solution containing the residual dehydrating agent and nucleoside H-phosphonate is removed from the carrier after each cycle by washing with an organic solvent such as acetonitrile. Thereafter, the protecting group is removed from the added nucleoside, preferably by treatment with a 2.5% vol/vol dichloroacetic acid/CH_2Cl_2 solution, although 1% w/v trichloroacetic acid/CH_2Cl_2 or ZnBr-saturated nitromethane also are useful. Other deprotection procedures suitable **for other known protecting groups** will be apparent to the ordinary artisan. (emphasis added)

With due respect, Applicants respectfully assert that the second sentence of the cited passage merely points out three specific deprotection reagents for use with the "triphenylmethyl ethers of the ribose or deoxyribose hydroxyl substituents" described in Froehler.[3] Further, the last sentence, which the Office Action considers "particularly instructive", merely states that other procedures for **other** known protecting groups will be apparent to those of skill in the art, but does not allude to what these protecting groups or procedures for their removal might be. Further, the cited passage appears to suggest that different procedures are required for "other" such protecting groups. Thus, it cannot be fairly said that cited passages in Froehler supports the proposition that a variety of deprotection solvent regimes are employed such that the skilled artisan would consider the choice of any particular deprotection solvent to be routine.

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[3] Applicants note in this regard that Froehler exemplifies only 5'-dimethoxytrityl protecting groups.

In view of the discussion above, Applicants respectfully assert that the teachings of the primary references, each taken individually or taken together as a whole, and contrary to the assertion of the Office Action (page 9 of the July 30, 2002 Office Action), do not "motivate the selection of practically any solvent mixtures which will dissolve the reactants and not otherwise interfere with the intended synthetic transformation."

The July 30, 2002 Office Action states on page 9 that the secondary references (the two cited Sproat et al. references, Conway et al. and Atkinson et al.) provide:

> ... disclosures that at least two different nucleoside 3'-O-phosphoramidites, at least one dinucleotide derivative, and some other nucleoside derivatives may be effectively dissolved in the aromatic hydrocarbon solvents benzene and/or toluene.

and further states that the disclosure of the solubility of such 3'-O-phosphoramidites, dinucleotide derivative, and "other" nucleoside derivatives provides:

> ... factually specific motivations for the ordinary practitioner conducting routine experimentation to substitute benzene, toluene, or their closely related aromatic solvent relatives as substitutes for at least a portion of the solvents typically used during the deprotection step in oligonucleotide synthesis."

Id. However, as discussed above, the central premise of the Office Action's argument is erroneous, because the primary references, each read as a whole, simply do not provide the motivation to substitute "any solvent that works" for the disclosed reagents.

Moreover, as apparently admitted by the Office Action, the secondary references merely provide solvents said to dissolve certain specific reagents used in

certain oligonucleotide synthetic protocols, but do not disclose the use of Applicants' claimed solvents for 5'-deprotection.

Where the basis of an obviousness rejection is that it would have been "obvious to try" the asserted combination or make the asserted modification to the prior art, *without the legally required teaching of motivation to make the combination or modification,* the rejection is improper. Applicants assert that the cited art does not provide the teaching or motivation asserted by the Office Action; i.e., that the cited art does not motivate the use of any and all solvents that are capable of working in a deprotection protocol. Without that teaching or motivation, the naked possibility that one could experiment with solvents and achieve Applicants' claimed invention is a rejection based on the impermissible "obvious to try" standard. As such, Applicants respectfully request that the rejection be withdrawn.

Claims 1-42 are rejected under 35 U.S.C.§103(a) for alleged obviousness over Horn et al., *Nucleic Acids Research* **1989**, *17*, 6959-6967 ("Horn CB"), in view of Horn et al., *Nucleosides and Nucleotides*, **25**, 4842-4849 (1997) ("Horn UA").

Applicants assert that one skilled in the art would not look to the branched oligonucleotide art for deprotection schemes for linear oligonucleotides. The Horn CB reference describes the synthesis of branched oligodeoxyribonucleotides. This reference states that the standard deprotecting reagent was found to be ineffective for deprotection of the synthesized branched DNA, and that trityl deprotection of such branched structures was achieved using 3% dichloroacetic acid in toluene. Applicants note that in the context of the present invention, i.e., synthesis of linear oligonucleotides, the occurrence of branched structures such as described in the Horn CB reference are contaminants to be avoided, and, in the event that such branch structures are produced, it is highly desirable to avoid deprotecting them, both to eliminate participation in further synthesis cycles, and

in order to utilize the trityl groups to eliminate the contaminant from the final purified linear oligonucleotide. Further, the Horn CB reference states at page 6965:

> In our early attempts to synthesize **branched DNA**, we found it difficult to deprotect the multiple intramolecular dimethoxytrityl functions with **standard DCA/CH_2Cl_2** even with extended exposure (2). Under the assumption that dimethoxytrityl stacking stabilize the protection, we employed 3% (v/v) DCA in toluene. With this solution it was possible to rapidly and efficiently detritylate the branched materials (Figure 2). (emphasis added)

Thus, the Horn CB reference teaches 1) that **deprotection with dichloroacetic acid in methylene chloride is *standard***; and that 2) the toluene solution was needed for deprotection of **branched DNA**, which posed particular problems. As such, Applicants assert that those of skill in the art would not be led to use the stringent deprotection regime disclosed in the Horn CB reference for standard synthesis of linear oligonucleotides.

The Horn UA reference teaches use of dichloroacetic acid in toluene/CH_2Cl_2 solvent in the context of the preparation of linear precursors of branched oliogmers. As discussed above, in this reference, a linear precursor is prepared, not cleaved from the solid support, and then converted to a branched product. In addition to not cleaving the linear product from the solid support as required by the instant claims, the Horn UA reference does not disclose the instantly claimed deprotection solvent. As amended, instant claims 1 and 21 preclude use of CH_2Cl_2 solvent. Because no motivation is found in either reference to cure these deficiencies, Applicants respectfully request that the rejection be withdrawn.

The Office Action has not set forth how any reference would have instructed the person of ordinary skill in the art to modify the reference teachings to afford the claimed invention. No reference teaches or fairly suggests deprotecting the 5'-hydroxyl group of a linear oligonucleotide, with a protic acid, in a solvent system

consisting essentially of an aromatic, alkyl aromatic, halogenated aromatic, halogenated alkyl aromatic, or aromatic ether solvent. Nor does any reference teach or fairly suggest to the person of ordinary skill in the art how to choose suitable deprotecting solvents from the myriad of possibilities. Absent these motivating factors, the Office Action has failed to establish that the person having ordinary skill in the art would have been motivated to substitute the an aromatic, alkyl aromatic, halogenated aromatic, halogenated alkyl aromatic, or aromatic ether solvent for the prior art dichloromethane, in the synthesis of linear oligonucleotides.

Applicants submit that the claims are in condition for allowance. An early Office Action to that effect is, therefore, earnestly solicited.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "VERSION WITH MARKINGS TO SHOW CHANGES MADE."

Respectfully Submitted,

John A. Harrelson, Jr.

Date: November 25, 2002

John A. Harrelson, Jr.
Registration No: 42,637

WOODCOCK WASHBURN LLP
One Liberty Place - 46th Floor
Philadelphia, PA 19103
Tel: (215) 568-3100
Fax: (215) 568-3439

VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the claims:

Claims 1, 21, and 42 have been amended as follows:

1. (Three Times Amended) A method for the preparation of a linear phosphorus-linked oligomer comprising the steps of:

(a) providing a solid support;

(b) attaching a 5'-O-protected nucleoside to the solid support;

(c) deprotecting the 5'-hydroxyl of the nucleoside with a deprotecting reagent comprising a protic acid in a solvent to deprotect the 5'-hydroxyl of the nucleoside, wherein the solvent consists essentially of [being] an aromatic solvent, an alkyl aromatic solvent, a halogenated aromatic solvent, a halogenated alkyl aromatic solvent, or an aromatic ether solvent;

(d) reacting the deprotected 5'-hydroxyl with an 5'-protected activated phosphorus compound to produce a covalent linkage therebetween;

(e) oxidizing or sulfurizing the covalent linkage to form a phosphodiester, phosphorothioate, phosphorodithioate or H-phosphonate linkage;

(f) repeating steps c through e at least once for subsequent couplings of additional activated phosphorus compounds, to produce the completed phosphorus-linked oligomer; and

(g) cleaving the oligomer from the solid support;

wherein steps (b) through (f) are performed with [using] an automated device;

wherein said oligomer is a linear oligomer.

21. (Twice Amended) A method for the preparation of a linear phosphorus-linked oligomer comprising the steps of:

(a) providing a solid support;

(b) attaching a 5'-O-protected nucleoside to the solid support;

(c) contacting the protected 5'-hydroxyl of the nucleoside with a deprotecting reagent comprising a protic acid in a solvent to deprotect the 5'-hydroxyl of the nucleoside, wherein the solvent consists essentially of [being] an aromatic solvent, an alkyl aromatic solvent, a halogenated aromatic solvent, a halogenated alkyl aromatic solvent, or an aromatic ether solvent;

(d) reacting the deprotected 5'-hydroxyl with a 5'-protected activated phosphite compound to produce a phosphite linkage;

(e) oxidizing or sulfurizing the phosphite linkage to form a phosphodiester, phosphorothioate, or phosphorodithioate linkage;

(f) repeating steps c through e at least once for subsequent couplings of additional activated phosphite compounds, to produce the completed phosphorus-linked oligomer; and

(g) cleaving the oligomer from the solid support;

wherein steps (b) through (f) are performed with [using] an automated device;

wherein said oligomer is a linear oligomer.

42. (Twice Amended) A method for the preparation of a linear phosphorus-linked oligomer comprising the steps of:

(a) providing a solid support;

(b) attaching a 5'-O-protected nucleoside to the solid support;

(c) deprotecting the 5'-hydroxyl of the nucleoside with a deprotecting reagent comprising dichloroacetic acid in toluene;

(d) reacting the deprotected 5'-hydroxyl with an 5'-protected activated phosphorus compound to produce a covalent linkage therebetween;

(e) oxidizing or sulfurizing the covalent linkage to form a phosphodiester, phosphorothioate, phosphorodithioate or H-phosphonate linkage;

(f) repeating steps c through e at least once for subsequent couplings of additional activated phosphorus compounds, to produce the completed phosphorus-linked oligomer; and

(g) cleaving the oligomer from the solid support;

wherein steps (b) through (f) are performed with [using] an automated device;

wherein said oligomer is a linear oligomer.